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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/035,596	03/05/98	GUNZBURG W	GSF98-01

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EXAMINER	
CHEN, S	
ART UNIT	PAPER NUMBER
1633	18

DATE MAILED: 08/15/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/035,596	GUNZBURG ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 May 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,9-14,16-19,23-28,31-33 and 36-94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,9-14,16-19,23-28,31-33 and 36-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' amendment filed 5-25-01 and substitute declaration filed 7-23-01 have been entered. Claims 4, 5, 29 and 30 have been canceled. Claims 1, 13, 23, 26, 47, 74, 79, 91 and 92 have been amended. Claims 1, 2, 9-14, 16-19, 23-28, 31-33 and 36-94 are pending.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 9, 14, 36, 44, 45, 55-57, 62, 76 and 84 remain rejected and claims 1, 2, 10-13, 16-19, 23-28, 31-33, 38, 66, 74, 75, 77-81, 91 and 92 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants' amendment filed 5-25-01 necessitates the rejection of claims 1, 2, 10-13, 16-19, 23-28, 31-33, 38, 66, 74, 75, 77-81, 91 and 92. Applicant's arguments filed 5-25-01 have been fully considered but they are not persuasive.

Applicants add the phrase "0.6 Kb PstI" in claims 1, 13, 23, 26, 74, 79, 91 and 92. Applicants argue that MMTV is a well known retrovirus and its genomic organization is also well known, and the description of the 0.6 Kb PstI promoter fragment in the U3 region of MMTV promoter is sufficient (amendment, page 4). This is not found persuasive because of the reasons of record and that there are various species of endogenous or exogenous MMTV

proviruses that have different MMTV promoter sequences. The specification only mention the term "U3" and the primers (D and E) used to amply the U3 region by PCR, but the specification fails to specify the nucleotide sequence of the U3 region and the 0.6 Kb PstI promoter fragment of MMTV promoter. The specification discloses there are two PstI site in the U3 region so that there is a 0.6 Kb PstI fragment, however Lefebvre shows only one PstI restriction site in the MMTV promoter disclosed (as pointed out by applicants on page 12 of amendment). Thus, the nucleotide sequence of MMTV promoter varies from species to species. Therefore, it is unclear what nucleotide sequence is intended for the phrase "U3 region of MMTV" or "0.6 Kb PstI MMTV promoter fragment".

Applicants argue that WAP promoter is well known in the art (amendment, page 5). This is not found persuasive because of the reasons of record.

3. Claims 37-40, 70-73, 92 and 94 remain rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MEP. § 2172.01. Applicants fails to provide arguments for this rejection.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 2, 9-14, 16-19, 23-28, 31-33 and 36-94 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for construction of vectors pMMTV-BAG and pWAP-BAG containing β-galactosidase gene under the control of MMTV and WAP, respectively, and the expression of β-galactosidase in explanted normal primary human mammary tissue infected with virus containing said vectors set forth above, does not reasonably provide enablement for any retroviral vector comprising any therapeutic gene under the control of a MMTV promoter or a WAP promoter and said therapeutic gene is expressed in a cell *in vivo,* a method of expressing said therapeutic gene in a human cell *in vivo*, any pharmaceutical composition comprising a DNA construct comprising any therapeutic gene under the control of a MMTV promoter or a WAP promoter, and a method for the treatment of human mammary carcinoma comprising administering to a human a retroviral particle expressing any therapeutic gene under the control of a MMTV or WAP promoter *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Applicant's arguments filed 5-25-01 have been fully considered but they are not persuasive.

Applicants argue that the specification has provided sufficient enabling disclosure for the claimed method and applicants' invention does not require the discovery of a new therapeutic gene and the determination of its function (amendment, page 6-7). This is not found persuasive because of the reasons of record and that the claims encompass any therapeutic gene, including unidentified gene, for gene therapy *in vivo*. The specification fails to provide correlation between

a therapeutic gene and a particular disease or disorder for gene therapy *in vivo*. The specification also fails to provide adequate guidance and evidence for the sufficient expression of any heterologous gene or any therapeutic gene under the control of any MMTV promoter or any WAP promoter in the retroviral vector or other vector for sufficient time *in vivo* such that therapeutic effects are provided for a particular disease or disorder, or for using said retroviral vector expressing any heterologous gene or therapeutic gene for the treatment of disorders or diseases of human mammary cells *in vitro* or *in vivo*.

Applicants argue that substitution of a known heterologous gene for beta-gal or cytochrome P450 gene is routine experimentation (amendment, page 7). This is not found persuasive because of the reasons of record and the reasons set forth above.

Applicants argue that Chen reference is clear evidence that applicants' *in vitro* beta-gal model correlates to the use of applicants' claimed constructs *in vivo* to treat human mammary carcinoma (amendment, page 8). This is not found persuasive because of the reasons of record (especially, page 14 of the Official action mailed 11-21-00, Paper No. 14) and the reasons set forth above.

Applicants argue that it is not required for applicants to prove what compounds or materials are safe, effective, and reliable for use in human, and Verma teaches adenoviral vector for short term expression of a gene. Applicants further argue that Eck discusses the successes seen with gene therapy protocols (amendment, page 8-9). This is not found persuasive because of the reasons of record and that although it is not necessary to prove safe use in human, the

specification must provide sufficient enabling disclosure for the claimed compositions, materials, or methods such that one skilled in the art at the time of the invention would know how to use the claimed invention. Further, Verma teaches that one major obstacle to success has been the inability to deliver genes efficiently and obtain sustained expression, and Eck reports several factors that can affect the gene transfer efficiency and those factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. In addition, gene therapy *in vivo* has to be considered on a case by case basis, a successful gene therapy can not be extrapolated into other successful gene therapies *in vivo* because of the unpredictability of the art at the time of the invention.

Applicants argue that Petitclerc indicates that expression of a heterologous gene will occur *in vivo* (amendment, page 9). This is not found persuasive because of the reasons of record. Petitclerc teaches that rabbit WAP promoter and MMTV LTR are highly efficient in directing gene expression *in vitro* in various cell lines but they are only moderate efficient in transgenic mice. Petitclerc points out that "the efficiency of transgene is in most cases largely unpredictable". Gene therapy *in vivo* encompasses *in vivo* expression of a heterologous gene in various organisms. It would be unpredictable whether a heterologous gene or a therapeutic gene would be expressed to obtain a sufficient amount for a sufficient duration of time *in vivo* to provide therapeutic effects for a gene therapy in a subject.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 2, 9-14, 16-19, 23-28, 31-33, 36, 74-81, 91 and 92 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Dranoff et al., 1993 (U2) in view of Lefebvre et al., 1991 (V2), Wilson et al., 1995 (X3), Archer et al., 1994 (U4), Gunzburg et al., WO 96/07748 (IDS-AQ) and Shao et al., 1994 (X2). Applicant's arguments filed 5-25-01 have been fully considered but they are not persuasive.

Applicants argue that the claims have been amended to specify the use of a 0.6 Kb PstI MMTV promoter fragment and Gunzburg reference was published after applicants' priority date, and Dranoff and Shao do not mention the MMTV promoter or the use thereof (amendment, page 12). This is not found persuasive because of the reasons of record and the following reasons:

Firstly, the foreign publication of the claimed priority, Denmark 0976/95, only discloses the use of U3-R-U5 structure that has the U3 region completely or partially deleted and replaced by polylinker containing WAP or MMTV regulatory sequence at **both** 5'LTR and 3'LTR. The claimed invention is directed to the use of **intact** U3-R-U5 at the 5'LTR region and a 3'LTR region comprising a completely or partially deleted U3 region and replaced by polylinker

containing MMTV regulatory sequence. Thus, the claimed invention is not supported by the specification of the foreign publication, Denmark 0976/95.

Secondly, the foreign publication of the claimed priority, Denmark 0976/95, only discloses the use of U3-R-U5 structure that has the U3 region completely or partially deleted and replaced by polylinker containing WAP or MMTV regulatory sequence at **both** 5'LTR and 3'LTR. The claimed invention is directed to the use of 0.6 Kb PstI MMTV promoter fragment. The specification fails to disclose the use of a 0.6 Kb PstI MMTV promoter fragment for constructing a retroviral vector, a retrovirus carrying a construct containing said 0.6 Kb fragment, a packaging cell line harbouring said retroviral vector, a capsule encapsulating said packaging cell line, a pharmaceutical composition containing said retroviral vector, and a method of treating human mammary carcinoma by using said retroviral vector. Thus, the claimed invention is not supported by the specification of the foreign publication, Denmark 0976/95. Therefore, the priority date of Denmark 0976/95 could not be applied to the cited reference Gunzburg et al., WO 96/07748.

Thirdly, although Dranoff and Shao do not mention the MMTV promoter or the use thereof, Lefebvre reveals the presence of MMTV promoter and the positive and negative regulatory regions upstreams of MMTV promoter. Wilson, Archer and Gunzburg teach using MMTV promoter in a transfection construct and the expression of downstream gene *in vitro*.

Fourthly, as discussed in the 112 second paragraph rejection, the nucleotide sequence of MMTV promoter varies from species to species, and it is unclear what nucleotide sequence is

intended for the phrase "0.6 Kb PstI MMTV promoter fragment". Since no specific nucleotide sequence is indicated in the claimed invention, it would have been obvious for one of ordinary skill at the time of the invention to use a 0.6 Kb MMTV promoter fragment according to the collective teachings of Dranoff, Lefebvre, Wilson, Archer, Gunzburg and Shao.

Applicants argue that Lefebvre teaches MMTV promoter having one PstI site but do not teach a 0.6 Kb PstI fragment of MMTV. Applicants further argue that Wilson and Archer also do not teach a 0.6 Kb PstI fragment of MMTV (amendment, page 12-13). This is not found persuasive because of the reasons set forth above and the reasons of record.

Conclusion

No claim is allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Kimberly Davis, whose telephone number is (703) 305-3015.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Deborah Clark

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